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Turner, Matthew, Mutter, Shaun T. ORCID logoORCID: <https://orcid.org/0000-0002-3995-0674>,  
Deeth, Robert J. and Platts, James A. (2018) Ligand field molecular dynamics simulation of  
Pt(II)-phenanthroline binding to N-terminal fragment of amyloid- peptide. PLoS One, 13 (3) .  
e0193668. ISSN 1932-6203 [Article] (doi:10.1371/journal.pone.0193668)

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RESEARCH ARTICLE

# Ligand field molecular dynamics simulation of Pt(II)-phenanthroline binding to N-terminal fragment of amyloid- $\beta$ peptide

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## OPEN ACCESS

**Citation:** Turner M, Mutter ST, Deeth RJ, Platts JA (2018) Ligand field molecular dynamics simulation of Pt(II)-phenanthroline binding to N-terminal fragment of amyloid- $\beta$  peptide. PLoS ONE 13(3): e0193668. <https://doi.org/10.1371/journal.pone.0193668>

**Editor:** Madepalli K. Lakshmana, Torrey Pines Institute for Molecular Studies, UNITED STATES

**Received:** November 17, 2017

**Accepted:** February 15, 2018

**Published:** March 6, 2018

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**Data Availability Statement:** Data generated in this study, in the form of DL\_POLY input and output files, are available from the Zenodo database (DOI: [10.5281/zenodo.1050387](https://doi.org/10.5281/zenodo.1050387)).

**Funding:** Work was funded in part by EPSRC (<https://www.epsrc.ac.uk/>) under grant ref EP/N016858/1. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

## Abstract

We report microsecond timescale molecular dynamics simulation of the complex formed between Pt(II)-phenanthroline and the 16 N-terminal residues of the A $\beta$  peptide that is implicated in the onset of Alzheimer's disease, along with equivalent simulations of the metal-free peptide. Simulations from a variety of starting points reach equilibrium within 100 ns, as judged by root mean square deviation and radius of gyration. Platinum-bound peptides deviate rather more from starting points, and adopt structures with larger radius of gyration, than their metal-free counterparts. Residues bound directly to Pt show smaller fluctuation, but others actually move more in the Pt-bound peptide. Hydrogen bonding within the peptide is disrupted by binding of Pt, whereas the presence of salt-bridges are enhanced.

## Introduction

Alzheimer's disease (AD) is one of the greatest healthcare challenges facing modern society.[1] Its aetiology is complex, but the importance of amyloid- $\beta$  (A $\beta$ ) peptides and their aggregation is well established.[2][3][4][5] AD is associated with formation of fibrils and plaques (dense, insoluble deposits of protein and cellular material outside and around neurons) in brain tissue that impair proper functioning of neurons. Plaques are formed by aggregation of A $\beta$  that are soluble in isolation, but insoluble when bound to one another. The presence of metals, notably copper, zinc and iron, is a vital part of the aggregation and subsequent toxicity of A $\beta$ : increased levels of Cu and Zn are found in plaque regions of diseased brain, [6][7] and those plaques which do not contain metal ions have been found to be non-toxic.[8] Moreover, platinum complexes inhibit aggregation,[9][10][11] opening new avenues for treatment and diagnosis. In these, ligand choice proves to be vital, with large planar aromatic groups acting to stabilise complexes between Pt and A $\beta$ . [9][12][13]

Structural details for naturally occurring metals such as Cu and Zn have been elucidated through a wide range of experimental [14][15] and simulation techniques,[16][17][18][19] but the equivalent for Pt is scarcer. Ma et al used HPLC, ESI-MS and NMR spectroscopy to examine the binding of Pt<sup>II</sup>-phenanthroline to A $\beta$ , suggesting that binding to His6 and His14 predominates and that  $\pi$ -stacking to aromatic residues Phe4, Tyr10 and His13 may also play a

role.[20][21] In addition, Streltsov et al used a combination of EXAFS and DFT to probe local binding environment at Pt and derive structural models for the interaction of platinum complexes with A $\beta$ 16 and A $\beta$ 42.[22] Recently, we showed that ligand field molecular mechanics (LFMM) [23][24][25] is an appropriate method to probe the binding of Pt to fragments of A $\beta$ , characterising the effect of Pt complexes on limiting conformational freedom of the peptide [26] and the role of ligand variation in complexes formed and 3D conformation adopted. [27] In this work, we extend this approach to examine the dynamical behaviour of a typical Pt-A $\beta$  adduct using molecular dynamics simulations and LFMM description of metal coordination coupled with conventional molecular mechanics (MM) for the peptide.

## Computational details

Molecular Dynamics simulations were carried out using a modified version of DL\_POLY 2.0 [28] that incorporates LFMM energies and forces.[29] Pt(A $\beta$ ) complexes were described using a combination of LFMM for Pt(II) [29][30] and AMBER94 [31] parameters for all other atoms. The A $\beta$ 1–16 peptide was built in extended conformation in MOE,[32] and protonation states at pH 7.4 assigned using the Protonate3D module of this package. Pt-phenanthroline complexes were bound to the peptide via His6-N $\epsilon$  and His14-N $\epsilon$ , as identified in our previous work.[26][27] Initial peptide conformations were selected from a LowMode Molecular Dynamics [33] simulation in MOE as reported previously. DL\_POLY input files were generated using DL\_FIELD [34] and the DommiMOE [24] extension to MOE.

For all simulations of the free A $\beta$  peptide, AMBER94 partial charges assigned by MOE were used. For Pt(phen)-A $\beta$  simulations, Merz-Kollman charges were calculated for model Pt(phen)-imidazole systems from HF/6-31G(d)/SDD electrostatic potential in Gaussian09,[35] with Pt<sup>II</sup> given a van der Waals radius of 2.0 Å (see ESI). The remaining peptide atoms were assigned AMBER94 charges as calculated by MOE.

Simulations were performed on isolated systems, with reaction field solvation in dielectric constant 78.4. Simulations were performed in the NVT ensemble, where temperature was controlled at 310 K using the Nosé-Hoover thermostat [36][37] with relaxation constant 0.5 ps. Equations of motions were integrated using a Verlet Leapfrog algorithm, with a timestep of 1 fs. The SHAKE algorithm [38] with tolerance  $10^{-8}$  Å was used to constrain bonds containing hydrogen. The vdW forces were calculated with a cutoff of 1 nm, while 2.1 nm was used as a cutoff for electrostatics. In each molecular dynamics trajectory, atomic positions and velocities were recorded every 500 fs and used for subsequent analysis.

Resulting MD trajectories were analysed using VMD, [39] with root mean square deviation (RMSD), radius of gyration, peptide secondary structure, hydrogen bonds, salt bridges, solvent accessible surface area and RMSF data recorded. The STRIDE algorithm [40], as implemented in VMD, was used to characterise each residue as either Turn,  $\beta$ -sheet,  $\beta$ -bridge,  $\alpha$ -helix,  $3_{10}$ -helix,  $\pi$ -helix or Coil- type structure.

## Results and discussion

Five simulations (labelled A-E) of the free A $\beta$ 16 fragment were carried out, each for 200 ns, along with five simulations (labelled F-J) for the Pt(A $\beta$ 16) system. Table 1 illustrates that all initial conformations are significantly different from one another, ensuring efficient sampling of the molecular phase space during simulations. Fig 1 shows an overlap of starting points of simulations F–J, showing the variation of backbone and sidechain conformations adopted. Equilibration of all ten simulations was monitored initially via the RMSD relative to starting points, as shown in Fig 2. Following recent work on A $\beta$ 40 [41] and A $\beta$ 42 [18], we consider that these simulations are ‘pseudo-equilibrated’ as RMSD fluctuates around a central point by

**Table 1. RMSD between starting points of free and platinated peptides.**

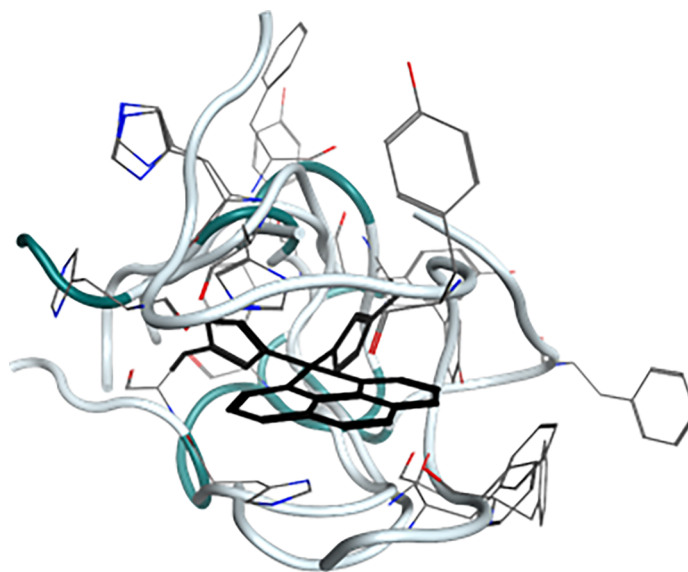
RMSD (Å)	A	B	C	D	E		F	G	H	I	J
A	-	2.140	4.420	6.459	8.213	F	-	7.605	6.334	7.485	6.323
B	-	-	4.310	6.362	8.259	G	-	-	6.400	3.301	5.949
C	-	-	-	5.488	7.261	H	-	-	-	5.774	5.807
D	-	-	-	-	5.763	I	-	-	-	-	5.797
E	-	-	-	-	-	J	-	-	-	-	-

<https://doi.org/10.1371/journal.pone.0193668.t001>

approximately 1 Å after a period of time taken as 80, 40, 10, 20 and 10 ns for A-E, 50, 25, 30, 25 and 25 ns for F-J, respectively. Simulation data beyond these points were used for further analysis.

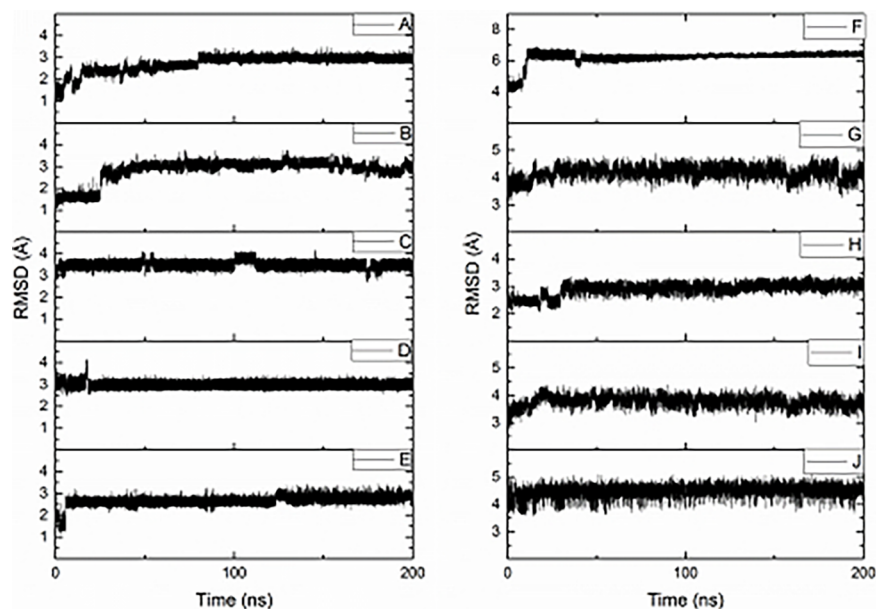
Table 2 summarises RMSD relative to the initial configuration for all ten sets of production MD runs. Free peptide values vary between 2.7 and 3.5 Å, with standard deviations in the range 0.1 to 0.2 Å, indicating relatively small movement from starting point and hence at least pseudo-equilibration of the individual simulations. Platinated peptides exhibit larger changes, equilibrating to between 3.0 and 6.3 Å, with maximum values also rather larger than those seen for the free peptide but standard deviations of similar magnitude, suggesting that these structures fluctuate to a similar degree. Moreover, RMSD values vary rather more between different simulations than within each one (A-E: mean = 3.03 Å, sd = 0.30 Å; F-J: mean = 4.36 Å, sd = 1.22 Å). This highlights the importance of using multiple starting points, since any one simulation reaches pseudo-equilibration relatively quickly and does not visit the entire configurational phase space available to the peptide.

Fig 3 shows radius of gyration ( $R_g$ ) data for ten simulations, with post-equilibration data summarised in Table 3. These show that the free Aβ16 fragment adopts a relatively compact structure, with  $R_g$  values typically less than 7 Å: for comparison, Aβ16 in an extended conformation has  $R_g$  of 16.99 Å, and in α-helical structure, 9.16 Å. Possible intra-molecular interactions that might give rise to these compact conformations are considered below. The standard



**Fig 1. Starting points of simulations F–J.** Pt(phen) aligned, backbone shown as tube, sidechains as wireframe and Pt(phen)(imid)<sub>2</sub> in black.

<https://doi.org/10.1371/journal.pone.0193668.g001>



**Fig 2. RMSD vs time for simulations A-J.**

<https://doi.org/10.1371/journal.pone.0193668.g002>

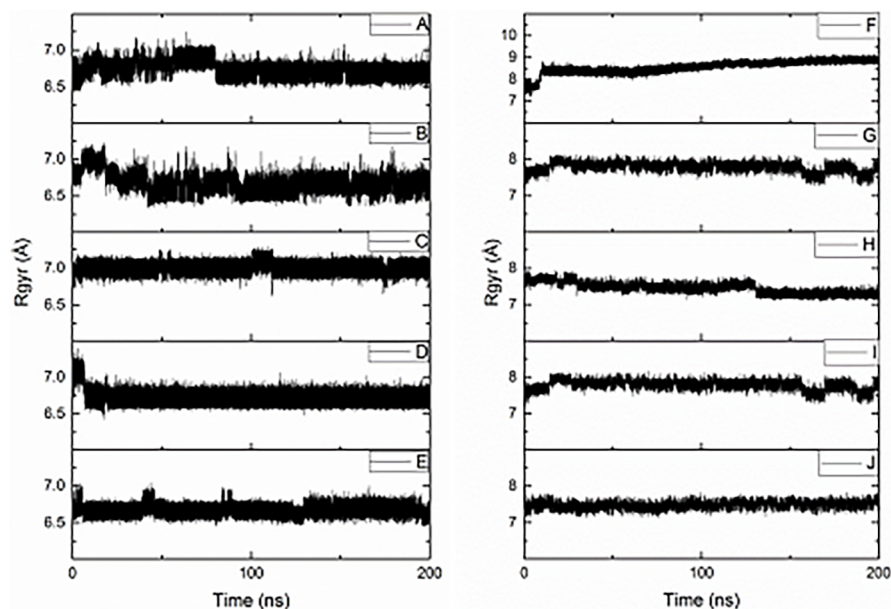
deviation within each simulation is also small, indicating that there is little change in the compactness of the peptide structure during any one simulation. In general, different simulations display a similar range of  $R_g$  values (A-E: mean = 6.74 Å, sd = 0.15 Å; F-J: mean = 7.83 Å, sd = 0.50 Å). This suggests that while the peptide as a whole remains compact, flexible peptide side-chains may be responsible for the similar degree of variation observed. However, simulation C has slightly larger average  $R_g$  value than the others: interestingly, C also displayed the greatest average RMSD value of the A $\beta$ 16 systems studied, suggesting that this simulation occupies a somewhat different configuration than the others.

Pt(A $\beta$ 16) simulations display significantly larger mean  $R_g$  values than their free peptide counterparts, indicating that coordination of the large, sterically demanding Pt-phen forces the structure to adopt less compact conformations. Standard deviation is consistent across these simulations, though slightly larger than for the free peptide systems. Pt(A $\beta$ 16) simulations are centred around 3 distinct  $R_g$  values, *ca.* 7.45 Å, 7.78 Å and 8.66 Å. F displays the

**Table 2. Mean, standard deviation, maximum and minimum RMSD relative to starting point for production MD data (Å).**

	Mean	SD	Min.	Max.
A	2.946	0.084	2.535	3.514
B	3.043	0.162	2.299	3.774
C	3.503	0.140	2.671	4.182
D	2.969	0.088	2.549	3.485
E	2.686	0.149	2.090	3.449
F	6.292	0.101	5.68	6.777
G	4.224	0.192	3.251	4.887
H	2.983	0.135	2.413	3.471
I	3.794	0.166	3.013	4.382
J	4.501	0.176	3.628	5.092

<https://doi.org/10.1371/journal.pone.0193668.t002>



**Fig 3. Radius of gyration of simulations A–J.**

<https://doi.org/10.1371/journal.pone.0193668.g003>

largest  $R_g$  of all Pt(A $\beta$ 16) simulations ( $8.66 \pm 0.2$  Å), significantly larger than all other conformations examined. Interestingly, this conformation displays a high prevalence of stabilising  $\pi$ - $\pi$  interactions (*vide infra*), which may cause the peptide backbone to extend and re-organise in order to accommodate these stacking arrangements. Simulations G and I display identical  $R_g$ : comparison of the final snapshot of the each trajectory shows that the structures are near-identical (RMSD = 0.11 Å compared with 3.30 Å at starting points), showing that the simulations converged to a common structure within the equilibration period.

Root mean square fluctuation (RMSF) of each residue was measured for production MD, as shown in Fig 4 (data from individual trajectories are shown in ESI). For the free peptide, large RMSF values are observed for Phe4, His6, Tyr10 and Val12, and small values for Asp1, Glu3, Arg5, and Glu11. Coordination of Pt(phen) at histidines 6 and 14 unsurprisingly reduces their RMSF, with Phe4 also moving less than in the metal-free case, whereas values for Tyr10, Val12 and Lys15 are on average larger after metallation. These data therefore suggest that coordination of Pt(phen) affects the peptide in more subtle ways than might first be thought, in

**Table 3. Mean, standard deviation, maximum and minimum radius of gyration for production MD data (Å).**

	Mean	SD	Min	Max
A	6.695	0.060	6.456	7.084
B	6.627	0.095	6.324	7.178
C	6.998	0.057	6.610	7.291
D	6.706	0.051	6.483	7.060
E	6.675	0.058	6.450	7.043
F	8.659	0.196	7.932	9.173
G	7.786	0.125	7.252	8.165
H	7.417	0.126	7.085	7.812
I	7.786	0.125	7.252	8.156
J	7.481	0.095	7.121	7.831

<https://doi.org/10.1371/journal.pone.0193668.t003>



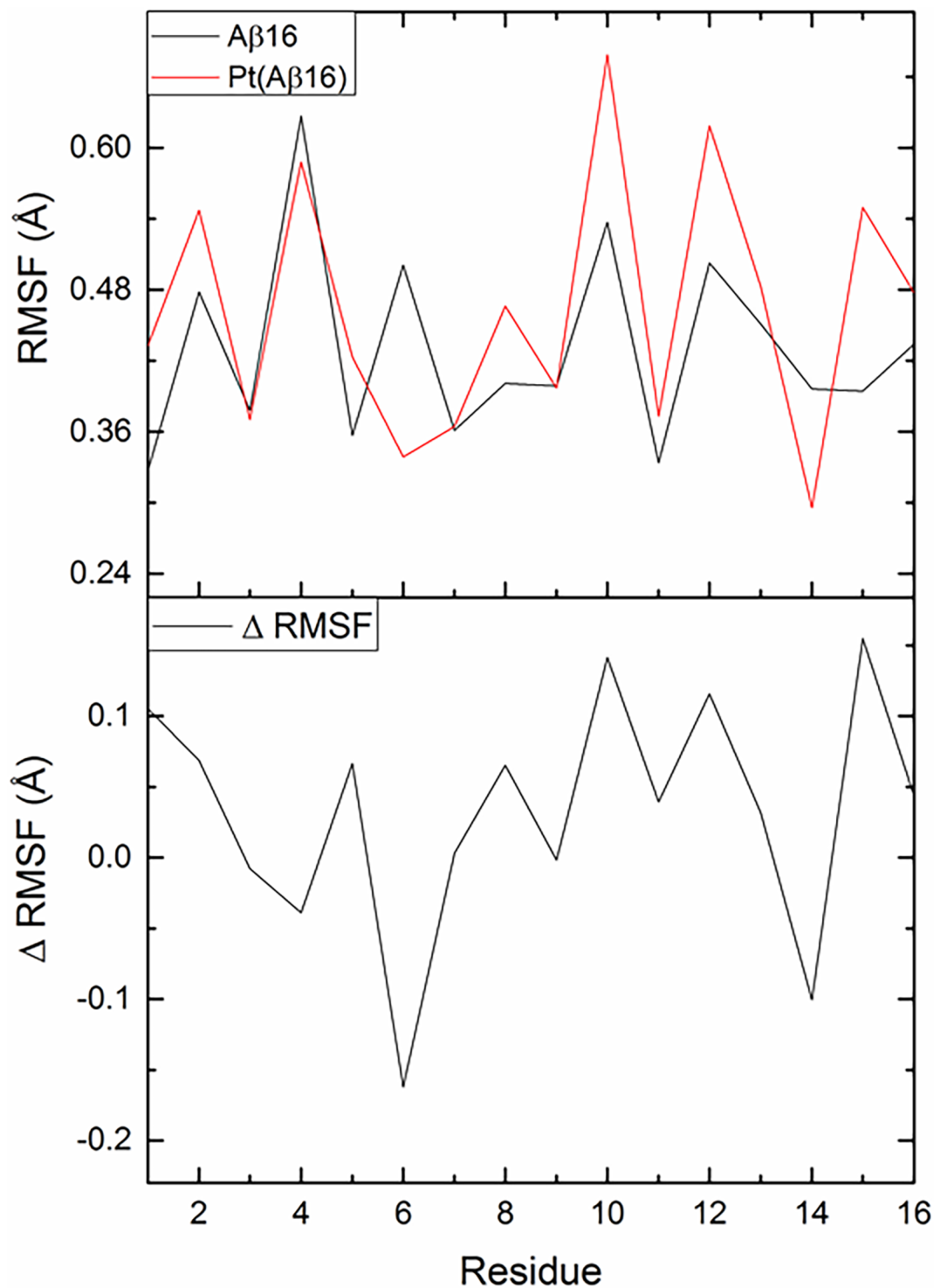
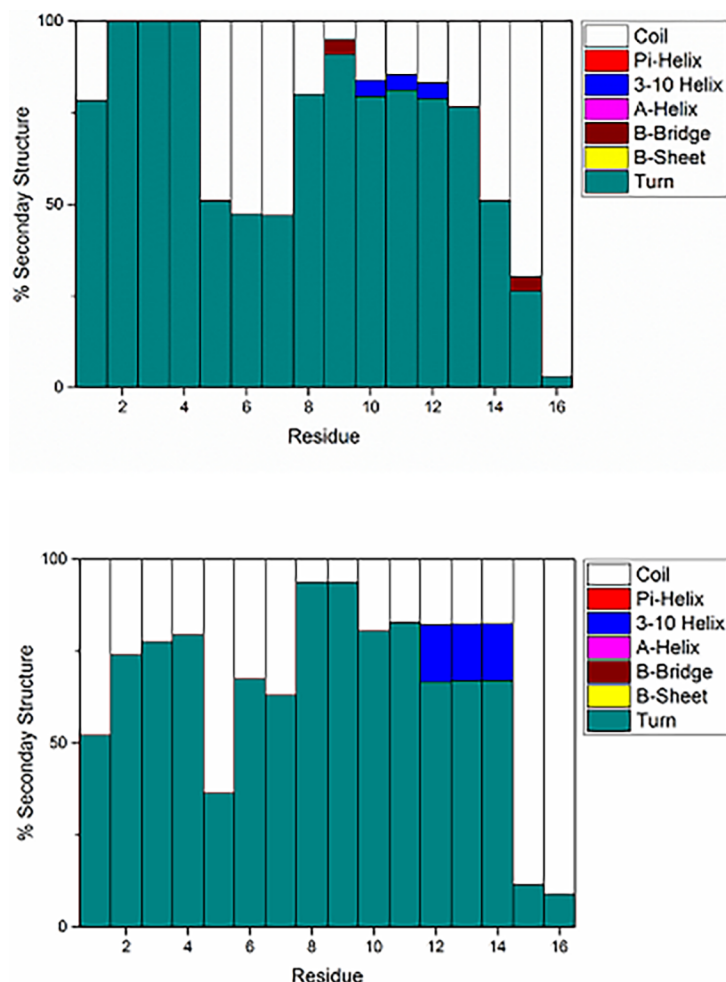


Fig 4. Average RMSF for A $\beta$ 16 and Pt(A $\beta$ 16), and the difference between average values.

<https://doi.org/10.1371/journal.pone.0193668.g004>

particular promoting more flexibility in residues lying between coordination sites. However, differences between free and Pt(phen) trajectories are of similar magnitude to those between repeat simulations. RMSF for Tyr10, for instance, is relatively constant at  $0.53 \pm 0.09$  Å over 5



**Fig 5. Percentage secondary structure of Aβ16 (top) and Pt(Aβ16) (bottom).**

<https://doi.org/10.1371/journal.pone.0193668.g005>

simulations of the free peptide, but varies rather more ( $0.67 \pm 0.31$  Å, max = 0.95 Å, min = 0.29 Å) for the equivalent Pt(phen) trajectories. Only three residues (His6, His14 and Gln15) exhibit differences in RMSF that exceed the sum of standard deviations: full details can be found in Supporting Information.

In addition, the effect of Pt<sup>II</sup>(phenanthroline) coordination on secondary structure was determined. Percentages of each type of structure over all simulations is shown in Fig 5, with numerical values reported in Supporting Information. As expected for an intrinsically disordered peptide, most residues in the free peptide adopt coil or turn conformations. Interestingly, there is a low propensity (4% of total simulation time) for residues Tyr10-Glu11-Val12 to form a 3 residue 3,10 helix, while residues Gly9 and Gln15 infrequently (4% of simulation) adopt β-bridge structures. The prevalence of turn and coil structures in these simulations is in good general agreement with most data for Aβ, though the propensity of residues to adopt turn structures is high. Other authors have noted that STRIDE has a greater tendency to assign turn structure than other secondary structure programs [42], but observed that most residues in Aβ exist as turn structure with approximately 30–80% probability. In addition, previous simulations of Aβ42 [42] displayed 3,10-helical structure for residues Tyr10-Val12 of approximately 3–5%, in agreement with our data.



Table 4. Mean, standard deviation, maximum and minimum number of hydrogen bonds in trajectories A–J.

	Mean	SD	Min	Max
(A)	6.43	1.99	0	16
(B)	5.61	1.86	0	14
(C)	7.05	1.86	0	17
(D)	7.11	2.06	0	17
(E)	5.78	1.81	0	15
(F)	5.70	1.66	0	13
(G)	5.15	1.74	0	13
(H)	3.86	1.64	0	12
(I)	5.15	1.75	0	12
(J)	5.95	1.78	0	13

<https://doi.org/10.1371/journal.pone.0193668.t004>

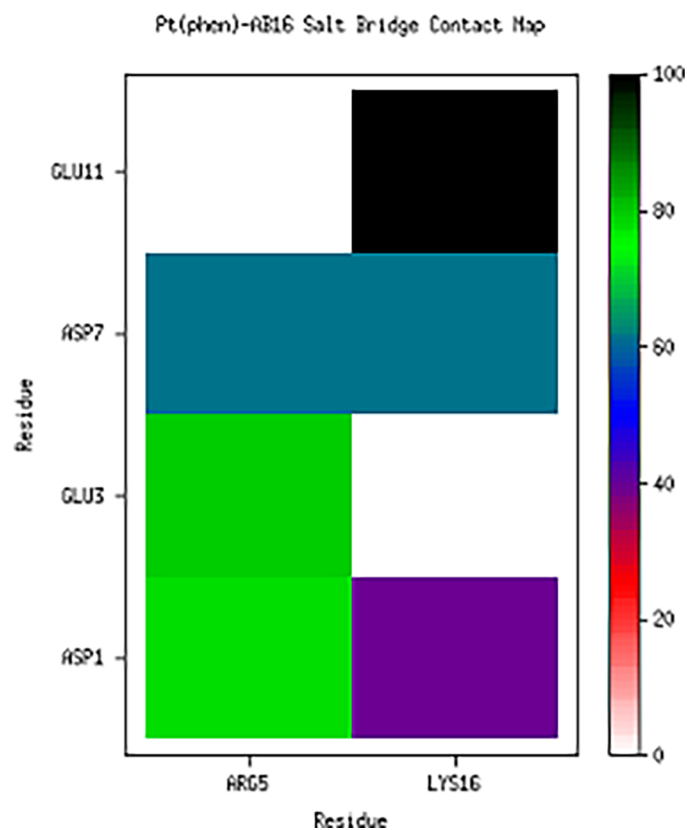
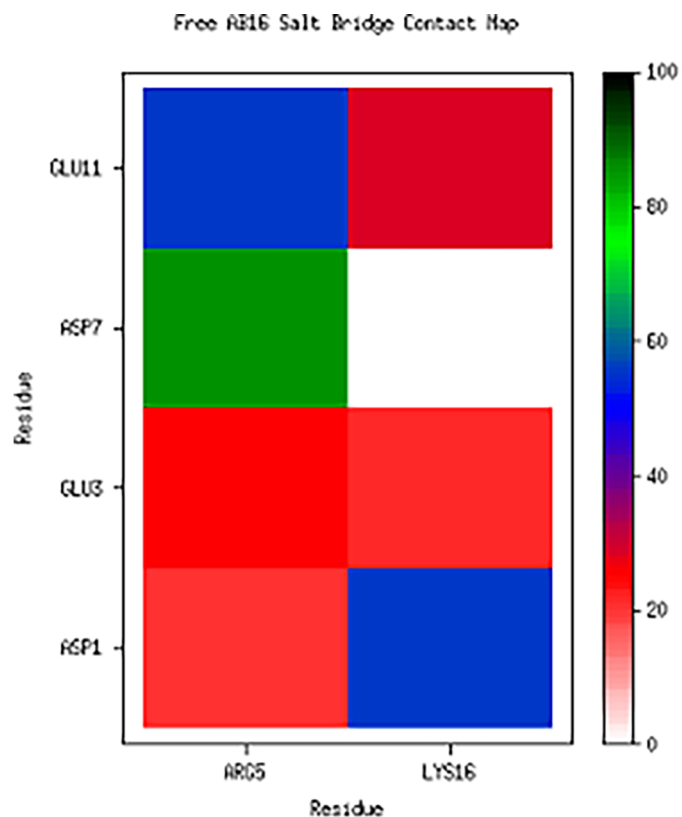
In the Pt(A $\beta$ 16) simulations, secondary structure is again predominantly assigned as either turn or coil, but the percentages of each secondary structure element differs from the free peptide. This indicates that coordination of Pt(phen) does not drastically change secondary structure, although Pt coordination shifts the 3<sub>10</sub>-helix towards the C-terminus and increases its incidence to 15% of total simulation time. Strikingly, residues involved in metal binding (His6, His14) show an increase in defined secondary structure (turn and helix) in the Pt(A $\beta$ 16) simulations, from approximately 50% in A $\beta$ 16 to 60–80% in the platinated system.

Hydrogen bond networks within free and platinated A $\beta$ 16 were also monitored (Table 4). In both cases there is a large variation across trajectories, with as few as zero and as many as 17 (free) or 13 (platinated) present in production data. In general, the Pt(A $\beta$ 16) systems show fewer hydrogen bonds than the free A $\beta$ 16 simulations, suggesting that the Pt(phenanthroline) system may interfere with the natural hydrogen bonding patterns of A $\beta$ 16. However, this difference is not significant, given the large standard deviations (~1.9–2.0) on the mean number of hydrogen bonds.

Intramolecular salt bridges, known to be important in the formation of fibrils,[43][44] were monitored during the course of the simulations. As the A $\beta$ 16 peptide fragment has two positively charged and four negatively charged residues, there are a total of eight possible salt bridge interactions. Each was monitored in VMD, defined as contact of less than 3.2 Å between O/N atoms in charged residues. Resulting data are summarised in Fig 6 and Table 5.

In the free A $\beta$ 16 peptide, Arg5 predominantly interacts with Asp7 (86% of frames) but also forms interactions with Glu11 (56%) and less frequently with Glu3 and Asp1. Lys16 forms salt bridges most frequently with Asp1 (56%), and also interacts with Glu3 and Glu11 (20–30%). In all trajectories, Lys16 never forms a salt bridge with Asp7. Binding of Pt(phen) induces clear changes in salt bridge structure: Arg5 still interacts with Asp7 but with reduced frequency (61%), and instead primarily interacts with Glu3 and Asp1 (*ca.* 80%), while no Arg5–Glu11 interactions are present. Lys16 forms a near-constant salt bridge with Glu11 (99%), as well as frequent interactions with Asp7 (62%) and Asp1 (40%). In contrast to the free peptide, Lys16 does not form a salt bridge at all with Glu3 in the Pt(A $\beta$ 16) simulations. Overall, Pt coordination causes Arg5 to switch from bridges with Asp7 and Glu11 to Glu3 and Asp1, while Lys16 salt bridges are formed with Glu11 and Asp7 instead of Asp1. It is notable that the combined percentage of observed salt bridge interactions exceeds 100%, indicating that residues are close enough to their charged partners to simultaneously form multiple salt bridge interactions.

$\pi$ - $\pi$  stacking interactions between ligand and aromatic side chains are thought to be important in targeting coordination to the N-terminus of A $\beta$ , as well as stabilising adducts. Close contacts between phen and side chains of Phe4, Tyr10 and His13 (defined as distance between



**Fig 6. Percentage of frames containing specified salt bridges, averaged over trajectories A–E (top) and F–J (bottom).**

<https://doi.org/10.1371/journal.pone.0193668.g006>

Cy and central C in phen) were monitored over simulations F–J. Distribution of these contacts are shown in Fig 7, showing that Phe4 in particular forms frequent  $\pi$ - $\pi$  interactions with the ligand, with a high distribution of contacts  $< 5$  Å. Tyr10 forms almost no  $\pi$ - $\pi$  interactions with the phenanthroline ligand, with only a few frames at distances of approximately 5–6 Å, while His13 shows moderate distribution of states where the  $\pi$ - $\pi$  inter-plane distance is less than 5 Å, sufficient for weak  $\pi$ - $\pi$  interaction. Of particular interest is simulation F, where both Phe4 and His13 simultaneously form  $\pi$ - $\pi$  stacking arrangements with the ligand for the final 150 ns of the simulation, with one residue above and below the ligand plane, as shown in Fig 8. These findings are in agreement with the findings of Ma et al [20][21], who reported stacking interactions with side chains of aromatic N-terminal residues, although the dynamical nature of our simulations reflect the highly flexible, intrinsically disordered nature of the A $\beta$  peptide.

## Conclusions

Molecular dynamics, using LFMM description of metal coordination coupled with AMBER description of peptide, elaborates details of the structure and properties of the complex formed between Pt-phenanthroline and the metal binding N-terminal fragment of amyloid- $\beta$  peptide. Using five distinct starting structures, along with analogous simulations of metal-free peptide, we find that simulations reach equilibration within a few tens of nano-seconds. Equilibrated data collected over more than 800 ns for metal-free and metallated peptides allow detailed comparison of size, secondary structure, and formation of hydrogen bonding and salt bridges.

Small changes in overall size and are observed on Pt binding, but rather larger differences in the mobility of individual residues, measured by root mean square fluctuation, occur. Changes in secondary structure, hydrogen bonding and salt-bridges on complexation of Pt are also observed: in general, His6 and His14 that are bound to Pt are less mobile and more structured than their Pt-free counterparts. Residues between these are slightly more mobile when bound, and exhibit slightly greater propensity to adopt turn and 3–10 helical structures. Hydrogen bonding is reduced by complexation, but salt bridges are more likely to form in the presence of Pt, while close contacts between phenanthrene ligand and aromatic residues Phe4, Tyr10 and His13 are present in at least some of the trajectories, with one structural motif of a sandwich of phenanthrene between Phe4 and His13 observed in a significant proportion of simulation time.

These studies represent first application of ligand field molecular dynamics (LFMD) to address the effect of platinum coordination on amyloid- $\beta$  structure and flexibility. Previous work from our group concentrated on validating the LFMM method against DFT and the small amount of experimental data available, and on use of conformational searching to examine the effect of variation in ligand structure. Here, we show for the first time that it is possible to quantify the effect of Pt on the dynamical landscape of A $\beta$  configurations adopted, showing

**Table 5. Percentage of frames containing specified salt bridges, averaged over all trajectories A–E and F–J.**

A $\beta$ 16	Asp1	Glu3	Asp7	Glu11
Arg5	20.99	25.93	85.64	55.88
Lys16	55.90	21.39	0.00	28.57
Pt(A $\beta$ 16)	Asp1	Glu3	Asp7	Glu11
Arg5	77.62	79.71	61.26	0.00
Lys16	39.57	0.00	61.91	99.44

<https://doi.org/10.1371/journal.pone.0193668.t005>

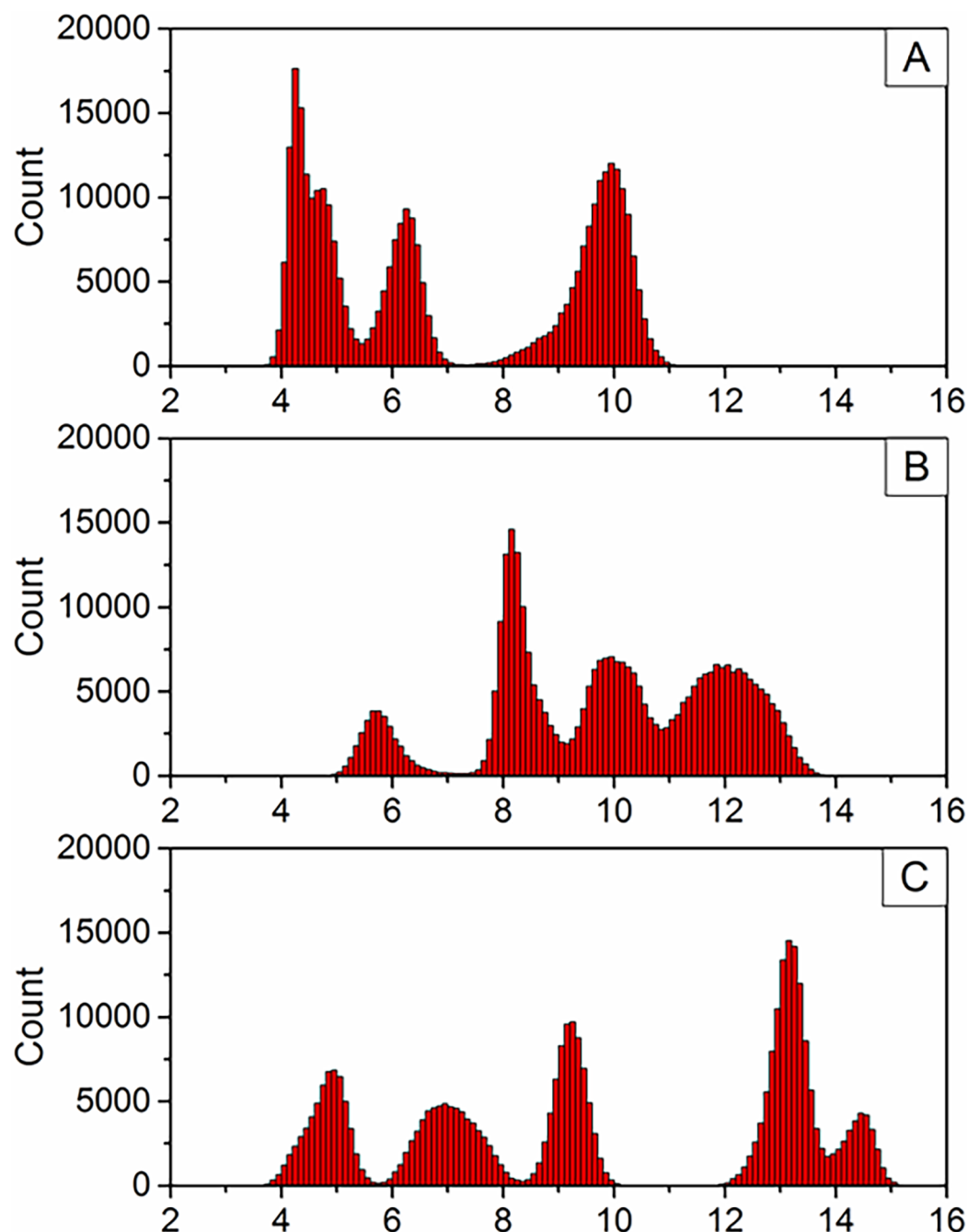
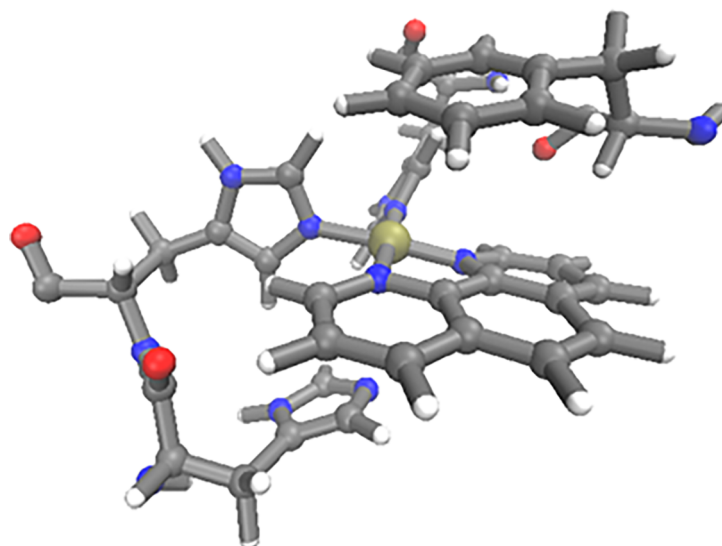


Fig 7. Distribution of phen contacts with (A) Phe4, (B) Tyr10 and (C) His13 (Å).

<https://doi.org/10.1371/journal.pone.0193668.g007>

that pseudo-equilibration of simulations is possible with relatively modest computational resources. In summary, microsecond timescale molecular dynamics quantifies the subtle but definite changes induced by coordination of Pt(phen) to the N-terminal portion of the amyloid- $\beta$  peptide. This fragment is widely used as a model for the full, biologically relevant peptides A $\beta$ 40 and A $\beta$ 42 and their interaction with metal ions: we intend to report analogous data for these peptides in due course.



**Fig 8.** Detail from final frame of trajectory F, showing close contact of Phe4 and His13 with phenanthroline.

<https://doi.org/10.1371/journal.pone.0193668.g008>

## Supporting information

### S1 Fig. Numbering of Pt(phen) region.

(TIF)

### S2 Fig. Starting conformations of free A $\beta$ 16 for simulations. Top row: A, B and C. Bottom row: D, E and F.

(TIF)

### S3 Fig. Superposition of starting conformations of free A $\beta$ 16.

(TIF)

### S4 Fig. Overlay of final snapshots of simulations G (grey) and I (yellow).

(TIF)

### S5 Fig. RMSF for A $\beta$ 16 simulations. A-E (top) and Pt(A $\beta$ 16) simulations F-J (bottom).

(TIF)

### S1 Table. Merz-Kollman partial charges for Pt(phen)(imid)<sub>2</sub>.

(PDF)

### S2 Table. RMSF details from individual simulations (Å).

(PDF)

### S3 Table. Percentage of secondary structures for simulations A–J.

(PDF)

## Acknowledgments

The authors are grateful to Advanced Research Computing @Cardiff (ARCCA) for use of super-computing resources.

## Author Contributions

**Conceptualization:** Matthew Turner, Robert J. Deeth, James A. Platts.

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**Formal analysis:** Matthew Turner, James A. Platts.

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## References

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc* 2007; 3:186–91. <https://doi.org/10.1016/j.jalz.2007.04.381> PMID: 19595937
2. Selkoe D. The Molecular Pathology of Alzheimers-Disease. *Neuron* 1991; 6:487–98. [https://doi.org/10.1016/0896-6273\(91\)90052-2](https://doi.org/10.1016/0896-6273(91)90052-2) PMID: 1673054
3. Haass C, De Strooper B. Review: Neurobiology—The presenilins in Alzheimer's disease—Proteolysis holds the key. *Science* 1999; 286:916–9. <https://doi.org/10.1126/science.286.5441.916> PMID: 10542139
4. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 2002; 416:535–9. <https://doi.org/10.1038/416535a> PMID: 11932745
5. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, et al. Natural oligomers of the amyloid-protein specifically disrupt cognitive function. *Nat Neurosci* 2005; 8:79–84. <https://doi.org/10.1038/nn1372> PMID: 15608634
6. Bush AI. The metallobiology of Alzheimer's disease. *Trends Neurosci* 2003; 26:207–14. [https://doi.org/10.1016/S0166-2236\(03\)00067-5](https://doi.org/10.1016/S0166-2236(03)00067-5) PMID: 12689772
7. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov* 2004; 3:205–14. <https://doi.org/10.1038/nrd1330> PMID: 15031734
8. Smith DP, Ciccotosto GD, Tew DJ, Fodero-Tavoletti MT, Johanssen T, Masters CL, et al. Concentration Dependent Cu<sup>2+</sup> Induced Aggregation and Dityrosine Formation of the Alzheimer's Disease Amyloid-β Peptide. *Biochemistry (Mosc)* 2007; 46:2881–91. <https://doi.org/10.1021/bi0620961> PMID: 17297919
9. Barnham KJ, Kenche VB, Ciccotosto GD, Smith DP, Tew DJ, Liu X, et al. Platinum-based inhibitors of amyloid-beta as therapeutic agents for Alzheimer's disease. *Proc Natl Acad Sci U S A* 2008; 105:6813–8. <https://doi.org/10.1073/pnas.0800712105> PMID: 18463291
10. Wang X, Wang X, Zhang C, Jiao Y, Guo Z. Inhibitory action of macrocyclic platiniferous chelators on metal-induced Aβ aggregation. *Chem Sci* 2012; 3:1304. <https://doi.org/10.1039/c2sc01100j>
11. Hureau C, Faller P. Platinoid complexes to target monomeric disordered peptides: a forthcoming solution against amyloid diseases? *Dalton Trans* 2014; 43:4233. <https://doi.org/10.1039/c3dt52954a> PMID: 24519324
12. Barnham KJ, Kenche VB, Hung LW, Perez K, Volitakes I, Ciccotosto G, et al. Development of a Platinum Complex as an anti-Amyloid Agent for the Therapy of Alzheimer's Disease. *Angew Chem-Int Ed* 2013; 52:3374–8. <https://doi.org/10.1002/anie.201209885> PMID: 23401085



13. Collin F, Sasaki I, Eury H, Faller P, Hureau C. Pt(II) compounds interplay with Cu(II) and Zn(II) coordination to the amyloid-beta peptide has metal specific consequences on deleterious processes associated to Alzheimer's disease. *Chem Commun* 2013; 49:2130–2. <https://doi.org/10.1039/c3cc38537j> PMID: 23386213
14. Kepp KP. Bioinorganic Chemistry of Alzheimer's Disease. *Chem Rev* 2012; 112:5193–239. <https://doi.org/10.1021/cr300009x> PMID: 22793492
15. Warmlander S, Tiiman A, A A, J L, J J, K I S, et al. Biophysical studies of the amyloid  $\beta$ -peptide: interactions with metal ions and small molecules. *Chembiochem Eur J Chem Biol* 2013; 14:1692–704. <https://doi.org/10.1002/cbic.201300262> PMID: 23983094
16. Alí-Torres J, Maréchal J-D, Rodríguez-Santiago L, Sodupe M. Three Dimensional Models of Cu<sub>2</sub>+-A $\beta$  (1–16) Complexes from Computational Approaches. *J Am Chem Soc* 2011; 133:15008–14. <https://doi.org/10.1021/ja203407v> PMID: 21846101
17. Alí-Torres J, Mirats A, Maréchal J-D, Rodríguez-Santiago L, Sodupe M. Modeling Cu<sub>2</sub>+-A $\beta$  complexes from computational approaches. *AIP Adv* 2015; 5:092402. <https://doi.org/10.1063/1.4921072>
18. Huy PDQ, Vuong QV, La Penna G, Faller P, Li MS. Impact of Cu(II) Binding on Structures and Dynamics of A $\beta$ 42 Monomer and Dimer: Molecular Dynamics Study. *ACS Chem Neurosci* 2016; 7:1348–63. <https://doi.org/10.1021/acscchemneuro.6b00109> PMID: 27454036
19. Raffa DF, Rauk A. Molecular Dynamics Study of the Beta Amyloid Peptide of Alzheimer's Disease and Its Divalent Copper Complexes. *J Phys Chem B* 2007; 111:3789–99. <https://doi.org/10.1021/jp0689621> PMID: 17388547
20. Ma G, Huang F, Pu X, Jia L, Jiang T, Li L, et al. Identification of [PtCl<sub>2</sub>(phen)] Binding Modes in Amyloid-beta Peptide and the Mechanism of Aggregation Inhibition. *Chem- Eur J* 2011; 17:11657–66. <https://doi.org/10.1002/chem.201101859> PMID: 21910144
21. Ma G, Wang E, Wei H, Wei K, Zhu P, Liu Y. PtCl<sub>2</sub>(phen) disrupts the metal ions binding to amyloid- $\beta$  peptide. *Metallomics* 2013; 5:879. <https://doi.org/10.1039/c3mt20262c> PMID: 23689733
22. Streltsov VA, Epa VC, James SA, Churches QI, Caine JM, Kenche VB, et al. Structural insights into the interaction of platinum-based inhibitors with the Alzheimer's disease amyloid-beta peptide. *Chem Commun* 2013; 49:11364–6. <https://doi.org/10.1039/c3cc47326k> PMID: 24161993
23. Burton V, Deeth R, Kemp C, Gilbert P. Molecular Mechanics for Coordination-Complexes—the Impact of Adding D-Electron Stabilization Energies. *J Am Chem Soc* 1995; 117:8407–15. <https://doi.org/10.1021/ja00137a014>
24. Deeth RJ, Fey N, Williams-Hubbard B. DommiMOE: An implementation of ligand field molecular mechanics in the molecular operating environment. *J Comput Chem* 2005; 26:123–30. <https://doi.org/10.1002/jcc.20137> PMID: 15584081
25. Deeth RJ, Anastasi A, Diedrich C, Randell K. Molecular modelling for transition metal complexes: Dealing with d-electron effects. *Coord Chem Rev* 2009; 253:795–816. <https://doi.org/10.1016/j.ccr.2008.06.018>
26. Turner M, Platts JA, Deeth RJ. Modeling of Platinum-Aryl Interaction with Amyloid- $\beta$  Peptide. *J Chem Theory Comput* 2016; 12:1385–92. <https://doi.org/10.1021/acs.jctc.5b01045> PMID: 26756469
27. Turner M, Deeth RJ, Platts JA. Prediction of ligand effects in platinum-amyloid- $\beta$  coordination. *J Inorg Biochem* 2017; 173:44–51. <https://doi.org/10.1016/j.jinorgbio.2017.05.003> PMID: 28494276
28. Smith W, Yong CW, Rodger PM. DL\_POLY: Application to molecular simulation. *Mol Simul* 2002; 28:385–471. <https://doi.org/10.1080/08927020290018769>
29. Tai H-C, Brodbeck R, Kasparkova J, Farrer NJ, Brabec V, Sadler PJ, et al. Combined Theoretical and Computational Study of Interstrand DNA Guanine-Guanine Cross-Linking by trans-[Pt(pyridine)<sub>2</sub>](2) Derived from the Photoactivated Prodrug trans,trans,trans-[Pt(N-3)(2)(OH)(2)(pyridine)(2)]. *Inorg Chem* 2012; 51:6830–41. <https://doi.org/10.1021/ic3005745> PMID: 22668523
30. Anastasi AE, Deeth RJ. Capturing the Trans Influence in Low-Spin d(8) Square-Planar Platinum(II) Systems using Molecular Mechanics. *J Chem Theory Comput* 2009; 5:2339–52. <https://doi.org/10.1021/ct9001569> PMID: 26616617
31. Cornell W, Cieplak P, Bayly C, Gould I, Merz K, Ferguson D, et al. A 2nd Generation Force-Field for the Simulation of Proteins, Nucleic-Acids, and Organic-Molecules. *J Am Chem Soc* 1995; 117:5179–97. <https://doi.org/10.1021/ja00124a002>
32. Molecular Operating Environment (MOE), (2013.08). 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7: Chemical Computing Group Inc.; 2013.
33. Labute P. LowModeMD—Implicit Low-Mode Velocity Filtering Applied to Conformational Search of Macrocycles and Protein Loops. *J Chem Inf Model* 2010; 50:792–800. <https://doi.org/10.1021/ci900508k> PMID: 20429574

34. Yong CW. Descriptions and Implementations of DL\_F Notation: A Natural Chemical Expression System of Atom Types for Molecular Simulations. *J Chem Inf Model* 2016; 56:1405–9. <https://doi.org/10.1021/acs.jcim.6b00323> PMID: 27455451
35. Frisch MJ, Trucks et al. GW. Gaussian09. Wallingford, CT: Gaussian Inc.; 2009.
36. Nosé S. A unified formulation of the constant temperature molecular dynamics methods. *J Chem Phys* 1984; 81:511–9. <https://doi.org/10.1063/1.447334>
37. Hoover WG. Canonical dynamics: Equilibrium phase-space distributions. *Phys Rev A* 1985; 31:1695–7. <https://doi.org/10.1103/PhysRevA.31.1695>
38. Ryckaert J-P, Ciccotti G, Berendsen HJC. Numerical integration of the cartesian equations of motion of a system with constraints: molecular dynamics of n-alkanes. *J Comput Phys* 1977; 23:327–41. [https://doi.org/10.1016/0021-9991\(77\)90098-5](https://doi.org/10.1016/0021-9991(77)90098-5)
39. Humphrey W, Dalke A, Schulten K. VMD: visual molecular dynamics. *J Mol Graph* 1996; 14:33–8, 27–8. PMID: 8744570
40. Frishman D, Argos P. Knowledge-based protein secondary structure assignment. *Proteins-Struct Funct Genet* 1995; 23:566–79. <https://doi.org/10.1002/prot.340230412> PMID: 8749853
41. Dong M, Li H, Hu D, Zhao W, Zhu X, Ai H. Molecular Dynamics Study on the Inhibition Mechanisms of Drugs CQ1–3 for Alzheimer Amyloid- $\beta$ 40 Aggregation Induced by Cu<sup>2+</sup>. *ACS Chem Neurosci* 2016; 7:599–614. <https://doi.org/10.1021/acschemneuro.5b00343> PMID: 26871000
42. Yang M, Teplow DB. Amyloid beta-Protein Monomer Folding: Free-Energy Surfaces Reveal Alloform-Specific Differences. *J Mol Biol* 2008; 384:450–64. <https://doi.org/10.1016/j.jmb.2008.09.039> PMID: 18835397
43. Nasica-Labouze J, Nguyen PH, Sterpone F, Berthoumieu O, Buchete N-V, Coté S, et al. Amyloid  $\beta$  Protein and Alzheimer's Disease: When Computer Simulations Complement Experimental Studies. *Chem Rev* 2015; 115:3518–63. <https://doi.org/10.1021/cr500638n> PMID: 25789869
44. Teplow DB, Lazo ND, Bitan G, Bernstein S, Wytttenbach T, Bowers MT, et al. Elucidating Amyloid  $\beta$ -Protein Folding and Assembly: A Multidisciplinary Approach. *Acc Chem Res* 2006; 39:635–45. <https://doi.org/10.1021/ar050063s> PMID: 16981680